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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/674,445 | 11/01/2000 | Jesus Prieto Valtuena | U013039-2 | 8974 |

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| EXAMINER | |
|---|---|
| SEHARASEYON, JEGATHEESAN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1647 | 15 |

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/674,445 | Applicant(s) PRIETO VALTUENA ET AL. | |
|---|---|---|---|
| | Examiner Jegatheesan Seharaseyon | Art Unit 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *11-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3 & 4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. This Office Action is in response to reply filed on the 3rd of March in Paper No: 14. Applicant's election with traverse of Group I is acknowledged. Applicant's remarks have been considered but are found to be persuasive and thus the restriction requirement is withdrawn. Therefore, all claims (11-27) will be included for the purpose of examination.

### *Specification*

2. The disclosure is objected to because of the following informalities:

(i) Throughout the specification Application refers to RNAm. It is presumed that this is mRNA.

Appropriate correction is required.

### *Drawings*

3. The draftsperson has objected to the figures (see PTO 948).

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4a. Claims 11, 16, 21, 22 and 23 are indefinite in that they only recite the polypeptide of interest by an arbitrary name. There is nothing in the claims that distinctly identifies the polypeptide. For example, others in the field may isolate and use the same protein, giving the said protein an entirely different name. Applicants should particularly point out

and distinctly claim the IFN α-5 polypeptide by sufficient identifying characteristics associated with the protein (e.g. amino acid sequence, molecular weight, etc.). Claiming biochemical molecules by a particular name given to the polypeptide by various workers in the field fails to distinctly claim what that protein is. Claims 12-14, 17-20 and 24-27 are rejected insofar as they depend on rejected claims 11, 16 and 23.

4b.Claim 11 is also vague and indefinite in the recitation of the term "lower than normal levels of IFN α-5". It is unclear how low level needs to drop before the administration of IFN α-5. It is presumed that there will be substantial variability in the normal levels of IFN α-5.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 21, 22 and 23 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a

disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The specification is insufficient to enable one skilled in the art to practice the claimed invention without an undue amount of experimentation. Applicant states that in liver tissue of patients infected with HCV there is marked reduction in the expression of the IFN α subtype normally expressed in liver tissue (page 19, lines: 6-8). This is presumably from the observations that in "normal" livers Applicant isolated more IFN α-5 clones, and in the liver tissue isolated from "HCV infected" patients the number of IFN α-5 clones was lower (Table 1). Applicant further speculates " it appears possible that the reduction in the expression of liver IFN α (IFN α-5) may play a part in making the HCV infection chronic" (page 19, lines; 15-18). Applicant's method of comparing the levels IFN α in normal liver versus the infected liver does not offer the skilled artisan a direct comparison of the levels of the messages because of the multiple steps involved. In addition, it is unclear what effect if any may be present at the level of translation or post translation. There is no indication that the assay accurately reflects the levels of IFN α-5 in the dynamic environment of a living subject. Thus, it is unclear if this method will be useful in assaying or screening in patients liver cells for diagnostic purposes. It

does not appear that there is a direct causality between liver diseases and IFN α-5. In addition, it is also unclear what's considered a normal level of IFN α-5. There is no guidance provided as to how much lower the expression of IFN α-5 needs to be in order to be "lower than normal". Furthermore, it is asserted that these observations may have therapeutic implications because of the antiviral and antiproliferative effect IFN α-5 (page 19, lines; 18-21). However, Applicant has not demonstrated the nexus between the possible administrations of IFN α-5 to treat liver disease of viral origin let alone HCV infection.

Applicant has not disclosed how to use the claimed invention to treat the liver diseases of viral origin patients (page 1, lines: 5-7). Applicant has only "shown" the lowering of IFN α-5 clones in the liver tissue from patients who have HCV infection, without treating affected subjects or shown an art recognized correlation between the data shown and the scope of the claimed invention. The artisan would recognize and appreciate that there is often no known correlation between *in vitro* and *in vivo* results, because the artisan recognizes that an *in vitro* assay cannot duplicate the complex conditions of *in vivo* treatment. In addition, variables such as biological stability, half-life, or clearance from the blood are important parameters in achieving successful therapy. Pharmaceutical therapies are unpredictable for the following reasons; (1) the proteins may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half life protein; (2) the protein may otherwise not reach the target area; (3) other functional properties,

known or unknown, may make the protein unsuitable for *in vivo use*, i.e. may produce adverse side effects prohibitive to the use of such treatment.

Since applicant has not provided any working examples of the efficacy of using IFN α-5 in treating already established disease subjects or demonstrated that *in vitro*, it would require an undue amount of experimentation to one of skill in the art to practice the claimed invention. There are no specific teachings in the disclosure that would allow one to have a reasonable expectation of success in transferring the IFN α-5 expression data to treat liver diseases of viral origin. One is only left with speculation and an invitation to experiment.

Given the breadth of claims 11, 21, 22 and 23, in light of the unpredictability of the art as determined by the lack of working examples, the level of skill of the artisan, and the lack of guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention for treating liver diseases of viral origin or screening for patients. In addition, due to the lack of established protocols for effective cytokine therapies, undue experimentation would be required to practice the claimed invention and would have little expectation of success.

***Claim Rejections - 35 USC § 102***

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6a. Claims 11-15, 21 and 23-27 rejected under 35 U.S.C. 102(b) as being anticipated by Foster et al. (1996).

The instant invention is directed to treating a patient having liver disease of viral origin with IFN α-5.

Foster et al. (1996) discloses the separation of the IFN α subtypes including IFN α -5 (abstract). It also teaches that interferons form a family of closely related cytokines with antiviral, antigrowth and immunostimulatory properties (Page 1027, 1st paragraph). These were tested in human tumor cell lines derived from liver, lung and neuroblast. Although Foster et al., does not explicitly teach the treatment of liver diseases of viral origin (Ex., HCV infection), the antiviral activity in liver cells is an inherent property of IFN α -5. Therefore, the disclosure of Foster et al. anticipates claims 11-15, 21 and 23-27.

6b. Claim11-15, 21 and 23-27 rejected under 35 U.S.C. 102(e) as being Foster et al. (U.S. Patent No: 6,007,805).

The instant invention is directed to treating a patient having liver disease of viral origin with IFN α-5.

Foster et al. (U. S. Patent No. 6,007,805) teaches the use of IFN α subtype in the preparation of a medicament (pharmaceutical formulation) for preventing or treating viral infections of a particular organ or cell type (column 2, lines 56-60). It also teaches that the particular IFN α subtype to be used in clinical practice will depend on the cell type that is infected (column 2, lines 5-7). It teaches that IFN α-5 has very potent antiviral activity in liver cells. It also demonstrates the relative ED50 for various interferon subtypes including IFN α-5 in three different cell lines (Fig 1A-1C). Although, it does not teach the specific virus such as HCV causing the disease or recite the diseases, the antiviral activity is an inherent property of IFN α-5. Therefore, the disclosure of Foster et al. anticipates claims 11-15, 21 and 23-27.

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7a. Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (1996) or Foster et al. (U.S. Patent No: 6,007,805) in view of Wallner et al. (U.S. Patent No: 5,914,111).

The instant invention is directed to treating a patient having liver disease of viral origin by administering recombinantly produced IFN $\alpha$-5.

The relevance of Foster et al. (1996) or Foster et al. (U.S. Patent No: 6,007,805) has been set forth above in paragraphs 6a and 6b. However, Foster et al. references do not explicitly recite the generation of IFN $\alpha$-5 protein using recombinant DNA methods. Wallner et al. discloses the generation of lymphocyte function associated antigen-3 (LFA-3) by recombinant methods. In particular it teaches the use of both prokaryotic host such as E.Coli and eukaryotic hosts including plant cells (column 11, lines 10-22). Furthermore, it also teaches the administration of the composition to patients (column 16, lines 25-32).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time invention was made to clone the gene encoding the IFN α-5 protein disclosed in Foster et al. references into suitable vectors for the expression in both prokaryotic and eukaryotic vectors for expression of recombinant protein, with a reasonable expectation of success, because Wallner et al. have demonstrated the recombinant expression LFA-3. It should also be noted at the time the invention was made cloning of genes into vectors for the expression in prokaryotic as well as eukaryotic host cells was routine in the art for the purpose of producing recombinant proteins. In addition, the recombinant IFN α-5 protein can also administered to a patient as claimed by Wallner et al. Therefore, the claims are obvious over Foster et al. (1996) or Foster et al. (U.S. Patent No: 6,007,805) in view of Wallner et al. (U.S. Patent No: 5,914,111).

7b. Claims 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (1996) or Foster et al. (U.S. Patent No: 6,007,805) in view of Wallner et al. (U.S. Patent No: 5,914,111) and further in view of Salmanian et al. (1996).

The instant invention is directed to treating a patient having liver disease of viral origin by administering recombinantly produced IFN α-5 in *Solanum tuberosum.*

The relevance of Foster et al. (1996) or Foster et al. (U.S. Patent No: 6,007,805) and Wallner et al. (U.S. Patent No: 5,914,111) has been set forth above in paragraphs 6a, 6b and 7a. However, Foster et al. and Wallner references do not explicitly recite the expression of IFN α-5 protein in *Solanum tuberosum* (potato). Salmanian et al.

discloses the expression of human epidermal growth factor protein in eukayrotic host *Solanum tuberosum* by recombinant methods (see abstract).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time invention was made to clone the gene encoding the IFN α-5 protein disclosed in Foster et al. references into suitable vectors for the expression in both prokaryotic and eukaryotic vectors for expression of recombinant protein as decribed by Wallner et al., with a reasonable expectation of success, because Salmanian et al. have demonstrated the recombinant expression human epidermal growth factor in *Solanum tuberosum* plants. It should also be noted at the time the invention was made cloning of genes into vectors for the expression in plants including *Solanum tuberosum* was routine in the art for the purpose of producing recombinant proteins. Therefore, the claims are obvious over Foster et al. (1996) or Foster et al. (U.S. Patent No: 6,007,805) in view of Wallner et al. (U.S. Patent No: 5,914,111) and further in view of Salmanian et al. (1996).

8. No claims are allowable.

**Contact Information**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JS
June 2, 2003

LORRAINE SPECTOR
PRIMARY EXAMINER